

Table S1. Comparison of response criteria

| | Imaging modality | Definition of target lesion | Response of target lesions | Progression of target lesions | Neurological signs and symptoms and steroids | Adaptations for immunotherapy |
|---------------------------|------------------|---|---|--|---|--|
| RECIST 1.1 ⁽¹⁾ | CT or MRI | unidimensional measured in at least one dimension 10 mm by CT scan number of target lesions : 5 | TARGET LESIONS - complete response Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm -partial response ≥30% decrease in the sum of diameters taking as reference the baseline sum diameters. | TARGET LESIONS ≥20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study + an absolute increase of at least 5 mm one or more new lesions is also considered progression. | not included | iRECIST ⁽²⁾ iUPD: immune unconfirmed progressive disease. iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (ie, target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria. new lesion: Results in iUPD but iCPD (immune confirmed progressive disease) is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD confirmation of progression: required Clinical stability is considered when deciding whether treatment is continued after iUPD |
| RANO-BM ⁽³⁾ | MRI | sum of the diameters for all target lesions measurable disease: at least one dimension, with a minimum size of 10 mm, and is visible on two or more axial slices that are preferably 5 mm or less apart with 0 mm skip the diameter perpendicular to the longest diameter in the plane number of target lesions : 5 | TARGET LESIONS - complete response disappearance of all CNS target lesions sustained for at least 4 weeks no new lesion -partial response ≥30% decrease in the sum longest diameter of CNS target lesions, taking as reference the baseline sum longest diameter sustained for at least 4 weeks no new lesion NON TARGET LESIONS - complete response disappearance of all enhancing CNS non-target lesions + no new CNS lesions - non-complete response/ non progressive disease: Persistence of one or more non-target CNS lesion or lesions. CLINICAL EVALUATION AND STEROIDS patient clinically stable or improved stable to decreased steroids dose | TARGET LESIONS ≥20% sum longest diameter of CNS target lesions taking as reference the smallest sum on study + an absolute increase of at least 5 mm new lesion NON TARGET LESIONS unequivocal progression of enhancing non-target CNS lesions new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumour-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease. CLINICAL EVALUATION AND STEROIDS worse steroids dose: not applicable | clinical evaluation at the discretion of the treating physician, IK from 90-100 to 70 or less; from 80 or less – 20; from any IK -50 an increase in steroid dose alone should not be used as a sole determinant of progression | iRANO ⁽⁴⁾ further immunotherapy treatment allowed after initial radiographic progressive disease (if clinically stable) pending disease progression confirmation if ≤6 months after start of immunotherapy a new lesion defines progressive disease if seen >6 months after start of immunotherapy repeat scan needed to confirm radiographic progressive disease for patients without significant clinical decline if ≤6 months after start of immunotherapy minimum time interval for confirmation of disease progression for patients without significant clinical decline ≥3 months yes if |

(1) Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur. J. Cancer 2009; 45(2):228–247

(2) Seymour L, Bogaerts J, Perrone A et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017; 18(3):e143–e152.

(3) Lin NU, Lee EQ, Aoyama H et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol. 2015; 16(6):e270-278.

(4) Okada H, Weller M, Huang R et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol. 2015; 16(15):e534–e542.

Table S2. Items collected in the CRF

| | |
|-----------------------|---|
| Inclusion criteria | pathological proof of melanoma (primary tumor or any metastasis) new diagnosis of BM BM measurable as defined by RANO criteria (10 x 5 mm) Initial treatment with immunotherapy alone (group 1), stereotactic radiosurgery (SRS) or hypofractionated RT alone or with non-immunotherapy systemic treatment combination (group 2), immunotherapy and SRS or hypofractionated SRT (group 3) |
| Demographic data | date of birth gender history of auto-immune disease history of allergies |
| Melanoma | date of initial diagnosis of melanoma initial location of melanoma Breslow index at melanoma diagnosis LDH level at melanoma diagnosis B-raf oncogene status presence of extra-CNS metastases at melanoma diagnosis date of locoregional progression extra-CNS metastases during the course of disease date of diagnosis of extra-CNS metastases presence of CNS metastases at melanoma diagnosis chemotherapy prior to the diagnosis of BM (and number of lines) targeted therapy prior to the diagnosis of BM (and number of lines) immunotherapy prior to the diagnosis of BM (and number of lines) systemic combination therapy prior to the diagnosis of BM (and number of lines) |
| Brain metastases (BM) | date of BM diagnosis spinal MRI at the time of BM diagnosis CSF analysis done at the time of BM diagnosis Karnofsky performance score at the time of BM diagnosis Neurological symptoms and signs at BM diagnosis (seizures, paresis, aphasia, visual disturbance, sensory deficit, headache, psychiatric and cognitive disorders, cerebellar and brainstem symptoms, other symptoms) LDH level History of metastatic site until BM diagnosis (locoregional, bones, liver, lung/pleura, mediastinal, cutaneous, gastro-intestinal, kidney, lymphadenopathy, other metastatic sites until BM diagnosis, other metastatic sites at BM diagnosis) Number of BM Maximum diameter of BM MRI presentation of BM (necrotic, cystic, hemorrhagic, significant edema defined by at 20% of the maximum diameter of BM) Treatment with anti-epileptic drugs, steroids (no, initiated at brain metastasis diagnosis, initiated at any time during the course of the disease) Surgery for BM (date, type, radiotherapy for surgical bed) Radiosurgery, fractionated stereotactic radiotherapy (number of target, dose volume treated) Systemic immunotherapy (date of initiation, type of immunotherapy, immunotherapy related AE leading to stop of immunotherapy) Systemic targeted therapy (date of initiation, type of targeted therapy) Systemic chemotherapy (date of initiation, type of chemotherapy) |
| Follow-up | at 3, 6, 9 and 12 months: Karnofsky performance score Neurological status as compared to initiation of brain metastases treatment MRI assessment for SRS targets as document by the treating oncologists MRI global assessment by the treating oncologists MRI scan availability MRI interpretation for SRT targets only according to RECIST 1.1 criteria if imaging available MRI interpretation for the whole brain according to RECIST 1.1 criteria if imaging available MRI interpretation for SRT targets only according to RANO criteria if imaging available MRI interpretation for the whole brain according to RANO criteria if imaging available MRI interpretation for SRT targets only according to iRANO criteria if imaging available |

| | |
|--|---|
| | MRI interpretation for the whole brain according to iRANO criteria if imaging available Evidence of pseudoprogression or radionecrosis Extra-CNS evaluation according to RECIST 1.1 Global evaluation (CNS + extra-CNS) Best MRI response Date of BM progression according to RANO criteria Type of CNS progression Pattern of brain progression Extra-CNS evaluation according to RECIST criteria at the time of brain progression Date of any first progression Type of any first progression Date of first extra-CNS progression Death Cause of death |
|--|---|

Table S3. Patient characteristics

| | All patients (n=62) | Group 1 Immunotherapy alone (n=10) | Group 2 Stereotactic radiotherapy without or with non-ICI pharmacotherapy (n=20) | Group 3 Immunotherapy plus stereotactic radiotherapy (n=32) |
|---|-------------------------|---|--|---|
| Melanoma history | | | | |
| Age at melanoma diagnosis in years: median (IQR) | 55 (43-64) | 57 (41-69) | 51 (41-60) | 57 (45-65) |
| Gender n (%) | | | | |
| - male | 39 (63) | 7 (70) | 13 (65) | 19 (59) |
| - female | 23 (37) | 3 (30) | 7 (35) | 13 (41) |
| History of immune disease (n, %) | | | | |
| - no | 55 (89) | 10 (100) | 19 (95) | 26 (81) |
| - yes | 6 (10) | 0 (0) | 0 (0) | 6 (19) |
| Unknown | 1 (2) | 0 (0) | 1 (5) | 0 (0) |
| History of allergy (n, %) | | | | |
| - no | 53 (85) | 10 (100) | 16 (80) | 27 (84) |
| - yes | 8 (13) | 0 (0) | 3 (15) | 5 (16) |
| - unknown | 1 (2) | 0 (0) | 1 (5) | 0 (0) |
| Location of primary melanoma (n, %) | | | | |
| - head and neck | 14 (23) | 5 (50) | 5 (20) | 4 (12) |
| - upper limbs | 11 (18) | 0 (0) | 3 (15) | 8 (25) |
| - lower limbs | 11 (18) | 3 (30) | 2 (10) | 6 (19) |
| - trunk | 19 (31) | 1 (10) | 8 (40) | 10 (31) |
| - mucosal | 1 (2) | 0 (0) | 1 (5) | 0 (0) |
| - unknown | 6 (10) | 1 (10) | 1 (5) | 4 (12) |
| Median Breslow index at melanoma diagnosis: median (IQR) | 3 (1.5-5.5) (n=52) | 6 (4-7) (n=8) | 3 (1-6.7) (n=18) | 2.5 (1.5-3.7) (n=26) |
| BRAF mutation (n, %) | | | | |
| - V600E mutation | 25 (40) | 3 (30) | 11 (55) | 11 (34) |
| - other BRAF mutation | 1 (2) | 0 (0) | 0 (0) | 1 (3) |
| - neither nor | 34 (55) | 7 (70) | 7 (35) | 20 (62) |
| - unknown | 2 (3) | 0 (0) | 2 (10) | 0 (0) |
| LDH level at primary melanoma diagnosis (n, %) | | | | |
| - increased | 6 (10) | 1 (10) | 2 (10) | 3 (9) |
| - normal | 16 (26) | 0 (0) | 3 (15) | 13 (41) |
| - no data | 40 (65) | 9 (90) | 15 (75) | 16 (50) |
| - median (IQR) | 347 (293-448) (n=21) | 293 (293-293) (n=1) | 473 (436-509) (n=4) | 328 (290-388) (n=16) |
| Distant metastasis at primary melanoma diagnosis (n, %) | | | | |
| - extra-CNS alone | 8 (13) | 0 (0) | 0 (0) | 8 (25) |
| - CNS alone | 4 (6) | 0 (0) | 0 (0) | 4 (12) |
| - both | 5 (8) | 1 (10) | 3 (15) | 1 (3) |
| - neither nor | 45 (72) | 9 (90) | 17 (85) | 19 (59) |
| Time interval between melanoma diagnosis and loco-regional PD in months: median (IQR) | 7.5 (2.8-29) (n=26) | 3 (2.8-10) (n=5) | 7 (4-15) (n=8) | 27 (2-36) (n=13) |
| Time interval between melanoma diagnosis and extra-CNS metastasis in months: median (IQR) | 14 (4.6-37.5) (n=52) | 11.9 (4.9-20.4) (n=10) | 16 (8-49) (n=15) | 12 (3-35) (n=27) |
| Sites of distant metastases prior to BM diagnosis (n, %) | | | | |
| - locoregional | 26 (42) (n=61) | 5 (50) | 9 (45) | 12 (37) (n=31) |
| - bones | 8 (13) | 3 (30) | 1 (5) | 4 (12) |
| - liver | 5 (8) | 1 (10) | 0 | 4 (12) |
| - lung/pleura | 20 (32) | 6 (60) | 5 (25) | 9 (28) |
| - mediastinal | 4 (6) (n=61) | 1 (10) | 1 (5) (n=9) | 3 (9) |
| - cutaneous | 24 (39) | 4 (40) | 5 (20) | 15 (47) |
| - gastrointestinal | 4 (6) | 0 | 1 (5) | 3 (9) |

| | | | | |
|---|---------|--------|--------------|---------|
| - kidney | 0 | 0 | 0 | 0 (0) |
| - lymphadenopathy | 4 (67) | 5 (50) | 12 (60) | 22 (69) |
| - other | 15 (24) | 1 (10) | 9 (45) (n=9) | 5 (16) |
| Treatment prior to BM diagnosis | | | | |
| Chemotherapy prior to the diagnosis of BM (n, %) | | | | |
| - yes | 6 (10) | 3 (30) | 0 (0) | 3 (9) |
| - no | 56 (90) | 7 (70) | 20 (100) | 29 (91) |
| Number of lines of chemotherapy prior to BM (n, %) | | | | |
| - none | 56 (90) | 7 (70) | 20 (100) | 29 (91) |
| - 1 | 6 (10) | 3 (30) | 0 | 3 (9) |
| - 2 | 0 | 0 | 0 | 0 |
| - >2 | 0 | 0 | 0 | 0 |
| Targeted therapy prior to the diagnosis of BM (n, %) | | | | |
| - yes | 8 (10) | 2 (20) | 2 (10) | 4 (12) |
| - no | 56 (90) | 8 (80) | 18 (90) | 28 (87) |
| Number of lines of targeted therapy prior to BM (n, %) | | | | |
| - none | 54 (87) | 8 (80) | 18 (90) | 28 (87) |
| - 1 | 7 (11) | 2 (20) | 1 (5) | 4 (12) |
| - 2 | 1 (2) | 0 (0) | 1 (5) | 0 (0) |
| - >2 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Immunotherapy prior to the diagnosis of BM (>90 days prior to SRT) (n, %) | | | | |
| - yes | 18 (29) | 4 (40) | 5 (25) | 9 (28) |
| anti-CTLA4 | 6 (10) | 1 (10) | 1 (5) | 4 (12) |
| anti-PD1 | 3 (5) | 0 (0) | 0 (0) | 3 (9) |
| interferon | 7 (11) | 2 (20) | 3 (15) | 2 (6) |
| anti-PD1 + interferon | 2 (3) | 1 (10) | 1 (5) | 0 (0) |
| - no | 44 (71) | 6 (60) | 15 (75) | 23 (72) |
| Number of lines of immunotherapy prior to BM (n, %) | | | | |
| - none | 44 (71) | 6 (60) | 15 (75) | 23 (72) |
| - 1 | 15 (24) | 3 (30) | 4 (20) | 8 (25) |
| - 2 | 3 (5) | 1 (10) | 1 (5) | 1 (3) |
| - >2 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Number of lines of any systemic treatment prior to BM (n, %) | | | | |
| - none | 36 (58) | 2 (20) | 15 (75) | 19 (59) |
| - 1 | 21 (34) | 7 (70) | 4 (20) | 10 (31) |
| - 2 | 4 (6) | 1 (10) | 0 (0) | 3 (9) |
| - >2 | 1 (2) | 0 (0) | 1 (5) | 0 (0) |

The number of patients is given when not all the data are available.

% among the whole cohort, unless specified

Abbreviations: BM: brain metastases, ICI: immune checkpoint inhibition, IQR: interquartile range, LDH: lactate dehydrogenase, n: number of patients, OS: overall survival, PFS: progression free survival, SRT: stereotactic radiotherapy

Table S4. Clinical and MRI follow-up

| Items | All patients (n=62) | Group 1 Immunotherapy alone (n=10) | Group 2 Stereotactic radiotherapy without or with non-ICI pharmacotherapy (n=20) | Group 3 Immunotherapy plus stereotactic radiotherapy (n=32) |
|---|------------------------|---|--|---|
| At 3 months | | | | |
| Survival status (n, %) | | | | |
| alive | 55 (89) | 7 (70) | 19 (95) | 29 (91) |
| deceased | 7 (11) | 3 (30) | 1 (5) | 3 (7) |
| lost to follow-up | 0 | 0 | 0 | 0 |
| Any progression prior to 3 months (n, %) | | | | |
| - yes | 17 (27) | 7 (70) | 4 (20) | 6 (19) |
| - no | 43 (69) | 3 (30) | 15 (75) | 25 (78) |
| - unknown | 2 (3) | 0 | 1 (5) | 1 (3) |
| Number of patients evaluable for MRI assessment at 3 months and without change of treatment (%) | 44 (71) | 3 (30) | 15 (75) | 25 (78) |
| KPS | 80 (80-90) (n=45) | 80 (80-90) (n=3) | 85 (77-90) (n=15) | 80 (80-100) (n=25) |
| Neurological status compared with initiation of BM treatment: n (% of evaluable patients) | | | | |
| - deteriorated | 7 (16) | 0 (0) | 4 (27) | 3 (12) |
| - stable | 31 (72) | 3 (100) | 8 (53) | 20 (80) |
| - improved | 5 (12) (n=43) | 0 (0) (n=3) | 3 (20) (n=15) | 2 (8) (n=25) |
| Steroid consumption: n (%) | | | | |
| - yes | 12 (30) | 1 (33) | 7 (50) | 4 (17) |
| - no | 28 (70) (n=40) | 2 (66) (n=3) | 7 (50) (n=14) | 19 (83) (n=23) |
| MRI assessment for SRS targets according to the treating oncologist | | n.a. | | |
| - progression | 6 (17) | | 2 (14) | 4 (18) |
| - stability | 15 (42) | | 6 (43) | 9 (41) |
| - improvement | 15 (42) (n=36) | | 6 (43) (n=14) | 9 (41) (n=22) |
| MRI global brain assessment according to the treating oncologist | | | | |
| - progression | 13 (29) | 1 (25) | 5 (33) | 7 (28) |
| - stability | 12 (27) | 1 (25) | 4 (27) | 7 (28) |
| - improvement | 19 (43) (n=44) | 2 (50) (n=4) | 6 (40) (n=15) | 11 (44) (n=25) |
| Extra-CNS evaluation | | | | |
| - progression | 13 (32) | 1 (33) | 3 (20) | 9 (39) |
| - stability | 17 (41) | 1 (33) | 6 (40) | 10 (43) |
| - improvement | 11 (27) (n=41) | 1 (33) (n=3) | 6 (40) (n=15) | 4 (17) (n=23) |
| Global evaluation | | | | |
| - progression | 18 (42) | 1 (33) | 5 (33) | 12 (48) |
| - stability | 14 (32) | 1 (33) | 5 (33) | 8 (32) |
| - improvement | 11 (26) (n=43) | 1 (33) (n=3) | 5 (33) (n=15) | 5 (20) (n=25) |
| At 6 months | | | | |
| Patients alive: n (%) | | | | |
| alive | 49 (79) | 5 (50) | 16 (80) | 28 (87.5) |

| | | | | |
|---|----------------------|------------------|---------------------|----------------------|
| deceased | 13 (21) | 5 (50) | 4 (20) | 4 (12.5) |
| Any progression prior to 6 months | | | | |
| - yes | 36 (58) | 9 (90) | 8 (40) | 19 (59) |
| - no | 24 (39) | 1 (10) | 11 (55) | 12 (19) |
| - unknown | 2 (3) | 0 (0) | 1 (5) | 1 (2) |
| Number of patients evaluable for MRI assessment at 6 months and without change of treatment (%) | 24 (39) | 1 (10) | 11 (55) | 12 (19) |
| KPS - median (IQR) | 80 (80-95) (n=23) | 80 (n=1) | 80 (80-97) (n=9) | 85 (77-92) (n=12) |
| Neurological status compared with initiation of BM treatment: n (%) | | | | |
| - deteriorated | 3 (13) | 1 (100) | 2 (20) | 0 (0) |
| - stable | 15 (65) | 0 (0) | 5 (50) | 10 (83) |
| - improved | 5 (22) (n=23) | 0 (0) (n=1) | 3 (30) (n=10) | 2 (17) (n=12) |
| Steroid consumption: n (%) | | | | |
| Yes | 6 (27) | 1 (100) | 5 (55) | 1 (8) |
| No | 15 (68) (n=22) | 0 (0) (n=1) | 4 (45) (n=9) | 11 (92) (n=12) |
| MRI assessment for SRS targets according to the treating oncologist: n (%) | | | | |
| - progression | 1 (5) | n.a. | 0 (0) | 1 (10) |
| - stability | 9 (45) | | 5 (50) | 4 (40) |
| - improvement | 10 (50) (n=20) | | 5 (50) (n=10) | 5 (50) (n=10) |
| MRI global brain assessment according to the treating oncologist: n (%) | | | | |
| - progression | 4 (17) | 1 (100) | 2 (18) | 1 (8) |
| - stability | 10 (42) | 0 (0) | 5 (45) | 5 (42) |
| - improvement | 10 (42) (n=24) | 0 (0) (n=1) | 4 (36) (n=11) | 6 (50) (n=12) |
| Extra-CNS evaluation: n (%) | | | | |
| - progression | 9 (39) | 1 (100) | 5 (50) | 3 (25) |
| - stability | 8 (35) | 0 (0) | 4 (40) | 4 (33) |
| - improvement | 6 (26) (n=23) | 0 (0) (n=1) | 1 (10) (n=10) | 5 (42) (n=12) |
| Global evaluation: n (%) | | | | |
| - progression | 8 (35) | 1 (100) | 5 (50) | 2 (16) |
| - stability | 8 (35) | 0 (0) | 3 (30) | 5 (42) |
| - improvement | 7 (30) (n=23) | 0 (0) (n=1) | 2 (20) (n=10) | 5 (42) (n=12) |
| At 9 months | | | | |
| Survival status: n (%) | | | | |
| alive | 38 (61) | 4 (40) | 15 (75) | 19 (59) |
| deceased | 24 (39) (n=62) | 6 (60) (n=10) | 5 (25) (n=20) | 13 (41) (n=32) |
| Progression prior to 9 months: n (%) | | | | |
| - yes | 46 (74) | 10 (100) | 15 (75) | 21 (65) |
| - no | 14 (22) | 0 (0) | 4 (20) | 10 (31) |
| - unknown | 2 (3) (n=62) | 0 (0) (n=10) | 1 (5) (n=20) | 1 (3) (n=32) |
| Number of evaluable patients (%) | 14 (22) | 0 | 4 (20) | 10 (31) |
| KPS - median (IQR) | 90 (80-90) (n=13) | n.a. | 85 (80-90) (n=4) | 90 (80-90) (n=9) |
| Neurological status compared with initiation of BM treatment: n (%) | | | | |
| - deteriorated | 0 (0) | n.a. | 0 (0) | 0 (0) |

| | | | | |
|--|-----------------------|----------|---------------------|----------------------|
| - stable | 11 (85) | | 3 (75) | 8 (89) |
| - improved | 2 (15) (n=13) | | 1 (25) (n=4) | 1 (11) (n=9) |
| Steroid consumption: n (%) | | | | |
| - yes | 2 (15) | n.a. | 1 | 1 |
| - no | 11 (85) (n=13) | | 3 (n=4) | 8 (n=9) |
| MRI assessment for SRS targets according to the treating oncologist: n (%) | | n.a. | | |
| - progression | 1 (8) | | 1 (25) | 0 (0) |
| - stability | 4 (33) | | 2 (50) | 2 (25) |
| - improvement | 7 (58) (n=12) | | 1 (25) (n=4) | 6 (75) (n=8) |
| MRI global brain assessment according to the treating oncologist: n (%) | | n.a. | | |
| - progression | 1 (8) | | 1 (25) | 0 (0) |
| - stability | 5 (38) | | 2 (50) | 3 (33) |
| - improvement | 7 (54) (n=13) | | 1 (24) (n=4) | 6 (66) (n=9) |
| Extra-CNS evaluation: n (%) | | n.a. | | |
| - progression | 2 (15) | | 1 (25) | 1 (11) |
| - stability | 5 (38) | | 2 (50) | 3 (33) |
| - improvement | 6 (46) (n=13) | | 1 (25) (n=4) | 5 (56) (n=9) |
| Global evaluation: n (%) | | n.a. | | |
| - progression | 2 (15) | | 1 (25) | 1 (11) |
| - stability | 5 (38) | | 2 (50) | 3 (33) |
| - improvement | 6 (46) (n=13) | | 1 (25) (n=4) | 5 (56) (n=9) |
| At 12 months | | | | |
| Survival status: n (%) | | | | |
| alive | 31 (50) | 4 (40) | 12 (60) | 15 (47%) |
| deceased | 31 (50) | 6 (60) | 8 (40) | 17 (53%) |
| Progression prior to 12 months: n (%) | | | | |
| - yes | 48 (61) | 10 (100) | 17 (85) | 21 (66) |
| - no | 12 (19) | 0 (0) | 2 (10) | 10 (31) |
| - unknown | 2 (3) | 0 (0) | 1 (5) | 1 (3) |
| Number of evaluable patients (% among initial number of patients) | 12 (19) | 0 | 2 (10) | 10 (31) |
| KPS - median (IQR) | 90 (85-100) (n=11) | n.a. | 95 (92-97) (n=2) | 90 (80-100) (n=9) |
| Neurological status compared with initiation of BM treatment: n (%) | | | | |
| - deteriorated | 1 (9) | n.a. | 0 (0) | 1 (11) |
| - stable | 8 (73) | | 1 (50) | 7 (78) |
| - improved | 2 (18) (n=11) | | 1 (50) (n=2) | 1 (11) (n=9) |
| Steroid consumption: n (%) | | | | |
| Yes | 0 (0) | | 0 (0) | 0 (0) |
| No | 9 (100) (n=9) | | 2 (100) (n=2) | 7 (100) (n=7) |
| MRI assessment for SRT targets according to the treating oncologist: n (%) | | n.a. | | |
| - progression | 0 (0) | | 0 (0) | 0 (0) |
| - stability | 3 (30) | | 0 (0) | 3 (37) |
| - improvement | 7 (70) (n=10) | | 2 (100) (n=2) | 5 (62) (n=8) |

| | | | | |
|--|------------------|------|------------------|-----------------|
| MRI global brain assessment according to the treating oncologist: n (%) | | n.a. | | |
| - progression | 1 (9) | | 0 (0) | 1 (11) |
| - stability | 3 (27) | | 0 (0) | 3 (33) |
| - improvement | 7 (64) (n=11) | | 2 (100) (n=2) | 5 (55) (n=9) |
| Extra-CNS evaluation: n (%) | | n.a. | | |
| - progression | 1 (9) | | 1 (50) | 0 (0) |
| - stability | 6 (54) | | 1 (50) | 5 (55) |
| - improvement | 4 (36) (n=11) | | 0 (0) (n=2) | 4 (44) (n=9) |
| Global evaluation: n (%) | | n.a. | | |
| - progression | 2 (18) | | 1 (50) | 1 (11) |
| - stability | 5 (45) | | 1 (50) | 4 (44) |
| - improvement | 4 (36) (n=11) | | 0 (0) (n=2) | 4 (44) (n=9) |

The number of patients is given when not all the data are available.

% among the whole cohort, unless specified

Abbreviations: BM: brain metastases, CNS: central nervous system, ICI: immune checkpoint inhibition, IQR: interquartile range, KPS: Karnofsky prognostic score, n: number of patients, OS: overall survival, PFS: progression free survival, SRT: stereotactic radiotherapy

Table S5. Response and prognosis according to initial BM MRI presentation

| Items | All patients (n=62) | Group 1 Immunotherapy alone (n=10) | Group 2 Stereotactic radiotherapy without or with non-ICI pharmacotherapy (n=20) | Group 3 Immunotherapy plus stereotactic radiotherapy (n=32) |
|---|------------------------|--|---|---|
| BM with a maximal diameter >30 mm (n, %) | 9 (14) (n=62) | 0 (n=10) | 5 (25) (n=20) | 4 (12) (n=32) |
| CR | 0 | 0 | 0 | 0 |
| Pseudoprogression | 0 | 0 | 0 | 0 |
| Radionecrosis | 2 (25) | 0 | 0 | 2 (50) |
| CNS PFS from first BM treatment in months (median, IQR) | 3 (2-6) (n=5) | 0 | 6 (4-9) (n=2) | 3 (2-4) (n=3) |
| OS from first BM treatment in months (median, IQR) | 13 (9-29) (n=9) | 0 | 17 (10-39) (n=5) | 8 (3-17) (n=4) |
| BM with a maximal diameter ≤30 mm (n, %) | 54 (87) (n=62) | 10 (100) (n=10) | 15 (75) (n=20) | 28 (87) (n=32) |
| CR | 6 (11) | 0 | 0 | 6 (21) |
| Pseudoprogression | 6 (11) | 0 | 3 (20) | 3 (11) |
| Radionecrosis | 5 (9) | 0 | 2 (10) | 3 (11) |
| CNS PFS from first BM treatment in months (median, IQR) | 4 (2-5) (n=35) | 2 (2-3) (n=10) | 5 (3-7) (n=11) | 4 (3-4) (n=14) |
| OS from first BM treatment in months (median, IQR) | 11 (6-25) (n=53) | 5 (3-21) (n=10) | 13 (5-15) (n=15) | 11 (7-29) (n=28) |
| Necrotic BM (n, %) | 5 (8) (n=59) | 0 (n=9) | 3 (15) (n=19) | 3 (9) (n=31) |
| CR | 0 | 0 | 0 | 0 |
| Pseudoprogression | 1 (20) | 0 | 1 (33) | 0 |
| Radionecrosis | 1 (20) | 0 | 0 | 1 (33) |
| CNS PFS from first BM treatment in months (median, IQR) | 4 (3-8) (n=4) | n.a. | 3 (3-4) (n=2) | 10 (6-13) (n=2) |
| OS from first BM treatment in months (median, IQR) | 14 (10-18) (n=6) | n.a. | 10 (9-14) (n=3) | 19 (1-24) (n=3) |
| Non-necrotic BM (n, %) | 44 (71) | 9 (90) (n=9) | 7 (35) (n=19) | 28 (87) |
| CR | 6 (10) | 0 | 0 | 6 (21) |
| Pseudoprogression | 5 (11) | 0 | 2 (28) | 3 (11) |
| Radionecrosis | 5 (11) | 0 | 2 (28) | 3 (11) |
| CNS PFS from first BM treatment in months (median, IQR) | 3 (2-5) (n=34) | 2 (2-3) (n=9) | 6 (3-10) (n=11) | 3 (3-4) (n=14) |
| OS from first BM treatment in months (median, IQR) | 11 (6-25) (n=56) | 7 (3-25) (n=9) | 13 (7-19) (n=19) | 10 (6-28) (n=28) |
| Cystic BM (n, %) | 8 (13) (n=61) | 0 (n=9) | 2 (10) (n=20) | 6 (19) (n=32) |
| CR | 1 (12) | 0 | 0 | 1 (17) |
| Pseudoprogression | 2 (25) | 0 | 0 | 2 (33) |
| Radionecrosis | 1 (12) | 0 | 0 | 1 (17) |
| CNS PFS from first BM treatment in months (median, IQR) | 4 (3-5) (n=5) | n.a. | 2 (n=1) | 4 (3-8) (n=4) |
| OS from first BM treatment in months (median, IQR) | 220 (13-31) (n=8) | n.a. | 39 (27-52) (n=2) | 20 (11-27) (n=6) |
| Non-cystic BM (n, %) | 53 (85) (n=61) | 9 (90) (n=9) | 18 (90) (n=20) | 26 (81) (n=32) |
| CR | 5 (9) | 0 | 0 | 5 (19) |
| Pseudoprogression | 4 (7) | 0 | 3 (17) | 1 (4) |
| Radionecrosis | 5 (9) | 0 | 2 (11) | 3 (11) |
| CNS PFS from first BM treatment in months (median, IQR) | 3 (2-5) (n=34) | 2 (2-3) (n=9) | 5 (4-9) (n=12) | 3 (3-4) (n=13) |
| OS from first BM treatment in months (median, IQR) | 11 (6-25) (n=53) | 7 (3-25) (n=9) | 12 (7-17) (n=18) | 10 (6-25) (n=26) |
| Hemorrhagic BM (n, %) | 19 (31) (n=58) | 1 (11) (n=9) | 5 (25) (n=18) | 13 (41) (n=31) |
| CR | 1 (5) | 0 | 0 | 1 (8) |
| Pseudoprogression | 1 (5) | 0 | 0 | 1 (8) |
| Radionecrosis | 1 (5) | 0 | 1 (20) | 0 |
| CNS PFS from first BM treatment in months (median, IQR) | 3 (2-4) (n=7) | 2 (2-2) (n=1) | 4 (3-5) (n=3) | 3 (3-4) (n=6) |
| OS from first BM treatment in months (median, IQR) | 9 (4-18) (n=19) | 3 (3-3) (n=1) | 10 (9-11) (n=5) | 8 (4-19) (n=13) |
| Non-hemorrhagic BM (n, %) | 39 (61) (n=58) | 8 (80) (n=9) | 13 (65) (n=18) | 18 (56) (n=31) |
| CR | 5 (13) | 0 | 0 | 5 (28) |
| Pseudoprogression | 5 (13) | 0 | 3 (23) | 2 (11) |
| Radionecrosis | 5 (13) | 0 | 1 (8) | 4 (22) |
| CNS PFS from first BM treatment in months (median, IQR) | 3 (2-5) (n=30) | 2 (1-4) (n=8) | 6 (3-10) (n=9) | 3 (3-4) (n=10) |
| OS from first BM treatment in months (median, IQR) | 14 (7-30) (n=39) | 9 (3-31) (n=8) | 14 (13-27) (n=13) | 16 (7-34) (n=18) |
| Significant edema (n, %) | 42 (68) (n=59) | 5 (50) (n=10) | 14 (70) (n=17) | 23 (72) (n=32) |
| CR | 4 (9) | 0 | 0 | 4 (17) |
| Pseudoprogression | 4 (9) | 0 | 3 (21) | 1 (4) |
| Radionecrosis | 3 (7) | 0 | 1 (7) | 2 (9) |
| CNS PFS from first BM treatment in months (median, IQR) | 3 (22-6) (n=24) | 2 (2-3) (n=5) | 5 (2-10) (n=9) | 4 (3-5) (n=10) |
| OS from first BM treatment in months (median, IQR) | 14 (6-27) (n=42) | 3 (3-7) (n=5) | 15 (13-25) (n=14) | 13 (6-27) (n=23) |
| Non-significant edema (n, %) | 17 (27) (n=59) | 5 (50) (n=10) | 3 (15) (n=17) | 9 (28) (n=32) |
| CR | 2 (12) | 0 | 0 | 2 (22) |
| Pseudoprogression | 2 (12) | 0 | 0 | 2 (22) |
| Radionecrosis | 3 (18) | 0 | 1 (33) | 2 (22) |
| CNS PFS from first BM treatment in months (median, IQR) | 6 (2-4) (n=16) | 2 (2-2) (n=5) | 5 (4-6) (n=4) | 3 (22-4) (n=7) |
| OS from first BM treatment in months (median, IQR) | 8 (4-14) (n=20) | 11 (2-25) (n=5) | 6 (4-9) (n=6) | 9 (7-1) (n=9) |

Abbreviations: BM: brain metastases, CNS: central nervous system, CR: complete response, ICI: immune checkpoint inhibition, IQR: interquartile range, KPS: Karnofsky prognostic

score, n: number of patients, OS: overall survival, PFS: progression free survival, PD: progressive disease, PR: partial response, SD: stable disease